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(54) **Pharmaceutical compositions containing non-steroidal anti-inflammatory agents**

(57) The invention relates to a pharmaceutical composition comprising a systemic non-streroidal anti-inflammatory drug together with the histamine H_2-antagonist 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol or a physiologically acceptable salt thereof. The histamine H_2-antagonist reduces gastric mucosal lesions caused by the anti-inflammatory drug.

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SPECIFICATION

Pharmaceutical compositions

This invention relates to improvements in the formulation of anti-inflammatory drugs.

Systemic non-steroidal anti-inflammatory drugs, such as aspirin, indomethacin and ibuprofen, are known to give rise to undesirable side effects. In particular, they are known to be ulcerogenic and can thus, for example, give rise to gastric ulceration when administered orally. This side effect may be further enhanced in combination with other factors such as stress. Since in some treatments these compounds may have to be used for an extended period, such side effects can prove a serious disadvantage.

British Specification Number 2,047,238 describes and claims 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol and its physiologically acceptable salts. This compound is a potent and long acting histamine H_2-antagonist which may be used in the treatment of conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration, and in the treatment of allergic and inflammatory conditions where histamine is a known mediator. It has now been discovered that mucosal lesions of the gastrointestinal tract caused by non-steroidal anti-inflammatory drugs can be significantly reduced by co-administering 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol.

The present invention provides a pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug and 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol or a physiologically acceptable salt thereof.

Particularly useful pharmaceutical compositions according to the invention are those in a form suitable for oral, rectal or transdermal administration.

The systemic non-steroidal anti-inflammatory drugs which may be employed in the invention generally also show analgesic activity and include, for example, aspirin, indomethacin, ibuprofen, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac and tolmetin. They may be used in the pharmaceutical compositions of the invention in their usual dosage amounts, e.g. 50 mg—1 g of aspirin, 10—100 mg of indomethacin, 5—50 mg of piroxicam and 100—500 mg of ibuprofen per dosage unit taken one or more times daily in accordance with the normal dosage regime for the drug in question.

It is preferred that 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol should be employed in the composition in the form of a physiologically acceptable salt. Such salts include salts of inorganic or organic acids such as the hydrochloride, hydrobromide, sulphate, acetate, maleate, succinate and fumarate salts. The hemisuccinate salt is particularly preferred. The amount of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol, preferably in the form of a physiologically acceptable salt, employed in the pharmaceutical composition of the invention will be an amount sufficient to reduce the gastrointestinal distress caused by the anti-inflammatory drug and will preferably be in the range of 1 to 100 mg, most preferably 3 to 40 mg, per dosage unit.

The pharmaceutical compositions of the invention may be presented in a conventional manner with the aid of at least one pharmaceutical carrier or excipient. The composition may take the form of, for example, tablets, capsules, powders, granules, solutions, syrups, suspensions or suppositories prepared by conventional means with acceptable excipients. The compositions may thus contain as excipients, for example, binding agents, compression aids, fillers, lubricants, disintegrants and wetting agents. If desired, other active ingredients may also be present in such compositions. Tablets may be coated in conventional manner, for example with a suitable film-forming material such as methyl cellulose, ethyl cellulose and/or hydroxypropylmethyl cellulose or with sugar. Liquid preparations may also contain, for example, edible oils such as peanut oil. Suppositories may contain, for example, fat-soluble or water miscible bases.

The pharmaceutical compositions for the invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the anti-inflammatory drug and 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol or its salt may be admixed, together if desired, with suitable excipients. Tablets may be prepared for example by direct compression of such a mixture. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine.

Alternatively, the pharmaceutical compositions of the invention may be presented in a suitable controlled release form so that the 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol or its salt is rapidly made available for absorption and the non-steroidal anti-inflammatory drug is released more slowly. The pharmaceutical compositions may thus be presented for oral or rectal administration in a conventional manner associated with controlled release forms.

The pharmaceutical compositions of the invention may be used in the treatment of inflammatory conditions, particularly acute and chronic musculo-skeletal inflammatory conditions such as rheumatoid and osteo-arthritis and ankylosing spondylitis, and for an analgesia in conditions such as dysmenorrhoea, especially where the use of the anti-inflammatory drug is limited by gastro-intestinal

side effects.

In order that the invention may be more fully understood, the following Examples are given by way of illustration only.

EXAMPLE 1

Tablets

(a)	mg/tablet
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	23.3*
Ibuprofen	400.00
Lactose	333.7
Hydroxypropyl methylcellulose	5.00
Sodium starch glycollate	30.00
Magnesium stearate	8.00
Compression weight	800.00

* Equivalent to 20 mg free base.

The 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4,-triazole-3-methanol hemisuccinate salt and ibuprofen are sieved through a 250 μm sieve and blended with the lactose. This mix is granulated with a solution of the hydroxypropyl methylcellulose. The granules are dried, screened and blended with the sodium starch glycollate and the magnesium stearate. The lubricated granules are compressed into tablets using 12.5 mm punches.

(b)	mg/tablet
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	23.3
Indomethacin	50.00
Microcrystalline cellulose	124.7
Magnesium stearate	2.00
Compression weight	200.00

The 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt and indomethacin are blended with the microcrystalline cellulose and magnesium stearate and compressed using 9.5 mm punches.

(c) The procedure of (a) above is used with the following:

	mg/tablet
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	11.65*
Ibuprofen	400.00
Lactose	345.35
Hydroxypropyl methylcellulose	5.00
Sodium starch glycollate	30.00
Magnesium stearate	8.00
Compression weight	800.00

* Equivalent to 10 mg free base.

(d) The procedure of (b) above is used with the following:

	mg/tablet
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	11.65
Indomethacin	50.00
Microcrystalline cellulose	136.35
Magnesium stearate	2.00
Compression weight	200.00

(e)

	mg/tablet
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	11.65
Piroxicam	20.00
Microcrystalline cellulose	116.85
Magnesium stearate	1.50
Compression weight	150.00

The 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt and piroxicam are blended with the microcrystalline cellulose and magnesium stearate and compressed using 8.0 mm punches.

EXAMPLE 2
Capsules

(a)	mg/capsule
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	23.3
Ibuprofen	400.00
Starch 1500**	273.7
Magnesium stearate	3.00
Fill weight	700.00

** A form of directly compressible starch supplied by Colorcon Ltd, Orpington, Kent.

The 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt and ibuprofen are sieved through a 250 μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 0 hard gelatin capsules using a suitable filling machine.

(b)	mg/capsule
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	23.3
Indomethacin	50.00
Starch 1500	125.7
Magnesium stearate	1.0
Fill weight	200.00

The 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt and indomethacin are sieved through a 250 μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 2 hard gelatin capsules using a suitable filling machine.

(c) The procedure of (a) above is used with the following:

	mg/capsule
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	11.65
Ibuprofen	400.00
Starch 1500	285.35
Magnesium stearate	3.00
Fill weight	700.00

(d) The procedure of (b) above is used with the following:

	mg/capsule
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	11.65
Indomethacin	50.00
Starch 1500	137.35
Magnesium stearate	1.0
Fill weight	200.00

(e)

	mg/capsule
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	11.65
Piroxicam	20.00
Lactose	117.60
Magnesium stearate	0.75
Fill weight	150.00

The 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt and piroxicam are sieved through a 250 μm sieve and blended with the lactose and magnesium stearate. The resultant mix is filled into size 3 hard gelatin capsules using a suitable filling machine.

EXAMPLE 3

Suppositories

(a)

	mg/suppository
1-methyl-5-[[3-[3-(1-piperidinylmethyl]phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	23.3
Ibuprofen	400.00
Adeps Solidus	556.7
Colloidal silica	20.00
Fill weight	1000.0

The 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt and ibuprofen are sieved through a 100 μm sieve and blended with molten Adeps Solidus containing colloidal silica. The resultant mixture is filled into suppository cavities using a suitable filling machine.

(b)

	mg/suppository
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	23.3
Indomethacin	100.00
Polyethylene glycol 400	50.00
Polyethylene glycol 4000	326.7
Fill weight	500.0

The 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt and indomethacin are sieved through a 100 μm sieve and blended with the molten polyethylene glycol mixture. The resultant mixture is filled into suppository cavities using a suitable filling machine.

(c) The procedure of (a) above is used with the following:

	mg/suppository
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	11.65
Ibuprofen	400.00
Adeps Solidus	568.35
Colloidal silica	20.0
Fill weight	1000.0

(d) The procedure of (b) above is used with the following:

	mg/suppository
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	11.65
Indomethacin	100.0
Polyethylene glycol 400	50.0
Polyethylene glycol 4000	338.35
Fill weight	500.00

(e) The procedure of (a) above is used with the following:

	mg/suppository
1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol hemisuccinate salt	11.65
Piroxicam	20.00
Adeps Solidus	453.35
Colloidal silica	15.00
Fill weight	500.00

CLAIMS

1. A pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug and 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol or a physiologically acceptable salt thereof.

2. A pharmaceutical composition as claimed in claim 1 in which the anti-inflammatory drug is aspirin, indomethacin, ibuprofen, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac or tolmetin.

3. A pharmaceutical composition as claimed in claim 1 or 2, also including at least one pharmaceutical carrier or excipient.

4. A pharmaceutical composition as claimed in any of claims 1 to 3 in a form suitable for oral or rectal administration.

5. A pharmaceutical composition as claimed in claim 4 in which the anti-inflammatory drug is indomethacin, ibuprofen or piroxicam.

6. A pharmaceutical composition as claimed in claim 5 which contains 10—100 mg of indomethacin, 100—500 mg of ibuprofen or 5—50 mg of piroxicam per dosage unit and 1—100 mg

of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol or a physiologically acceptable salt thereof per dosage unit.

7. A pharmaceutical composition as claimed in claim 6 which contains 3 to 40 mg of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol or a physiologically acceptable salt thereof per dosage unit.

8. A pharmaceutical composition as claimed in any of claims 1 to 7 in which the 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol is used in the form of the hemisuccinate salt.

9. A method for the manufacture of a pharmaceutical composition which comprises processing a systemic non-steroidal anti-inflammatory drug and 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]-propyl]amino]-1H-1,2,4-triazole-3-methanol or a physiologically acceptable salt thereof to form a pharmaceutical composition.

10. A method as claimed in claim 5 wherein the anti-inflammatory drug is aspirin, indomethacin, ibuprofen, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac or tolmetin.

11. A method as claimed in claim 9 or 10 wherein the active ingredients are processed together with at least one pharmaceutical carrier or diluent.

12. A method as claimed in any of claims 9 to 11 wherein the active ingredients are processed into a pharmaceutical composition in a form suitable for oral or rectal administration.

13. A method as claimed in claim 12 in which the anti-inflammatory drug is indomethacin, ibuprofen or piroxicam.

14. A method as claimed in claim 13 in which the anti-inflammatory drug and the 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol or the physiologically acceptable salt thereof are used in amounts such that the composition produced contains 10—100 mg of indomethacin, 100—500 mg of ibuprofen or 5—50 mg of piroxicam per dosage unit and 1—100 mg of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol or a physiologically acceptable salt thereof per dosage unit.

15. A method as claimed in claim 14 in which the composition produced contains 3 to 40 mg of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol or a physiologically acceptable salt thereof per dosage unit.

16. A method as claimed in any of claims 9 to 15 in which the 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol is used in the form of the hemisuccinate salt.

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